

An efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation using a heterogeneous catalyst under solvent-free conditions

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Abstract

An efficient Hantzsch condensation of polyhydroquinoline derivatives was reported via a four-component coupling reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of $\text{HClO}_4\text{-SiO}_2$ under solvent-free conditions. Operational simplicity, use of an economically convenient catalyst, high yield, short reaction times are the key features of this protocol.

Keywords: $\text{HClO}_4\text{-SiO}_2$, Hantzsch condensation, one-pot synthesis, polyhydroquinoline derivatives

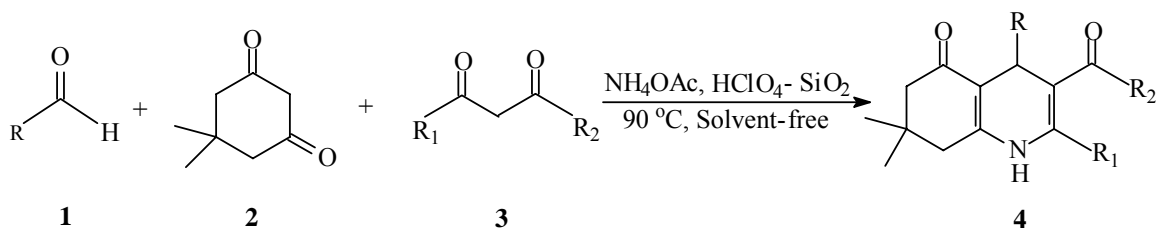
Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers and emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension.¹ 1,4-Dihydropyridines possess a variety of biological activities, such as, vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agent.^{2a-d} Recent studies have revealed that 1,4-DHPs exhibit several medicinal applications which include neuroprotectant^{3a} and platelet anti-aggregatory activity,^{3b} in addition cerebral antiischemic activity in the treatment of Alzheimer's disease^{3c} and as chemo sensitizer in tumor therapy.^{3d} These examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database showed the DHP framework to be among the most prolific chemo-types found. Development of drug resistance, both intrinsic drug resistance and acquired drug resistance, remains a clinical obstacle in the chemotherapy of many cancers.⁴⁻⁵ Among the possible resistance modifiers, the dihydropyridines, calcium antagonists, have been studied extensively as the analogue of

verapamil.⁶ Furthermore, the photocatalytic oxidation of these compounds to pyridines has been intensively investigated.⁷ Relatively speaking 1,4-dihydropyridine derivatives combined with a single ring have been mostly reported. Thus, the synthesis of the heterocyclic nucleus is of continuing interest.

In view of the importance of polyhydroquinoline derivatives, many classical methods for their synthesis were reported⁸⁻¹³ using conventional heating and refluxing approaches in the presence of an organic solvent. These methods, however, involves long reaction times, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally leading to low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-dihydropyridines and the progress in this field is remarkable including recently the promotion of microwave,¹⁴ TMSCl,¹⁵ ionic liquids,^{16,17} polymers^{18,19} and Yb(OTf)₃.²⁰ Moreover, to the best of our knowledge no report has been made so far about the use of HClO₄-SiO₂ as catalyst in the Hantzsch condensation. Recently HClO₄-SiO₂ has been used to catalyze the acetylation of alcohols and phenols using acetic acid.²¹ The multi-component reactions are powerful tools in the modern drug discovery process and allow fast, automated and high throughput generation of organic compounds.²² The possibility of performing multi-component reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view. In recent years heterogeneous catalysts are gaining more importance due to environmental-economic factors. The catalyst is generally of low cost and can be easily handled or removed.

Herein, we would like to report a facile Hantzsch condensation in the presence of a heterogeneous catalyst under solvent-free conditions, using substituted aldehydes (**1**), dimedone (**2**), ethyl acetoacetate (**3**) and ammonium acetate to produce the polyhydroquinoline derivatives (**4**) in excellent yields.



Scheme 1

Results and Discussion

The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxyl, halides and olefins under the reaction conditions. Thus, we have selected the optimized reaction conditions to examine the generality of this catalyst application. Various aromatic, aliphatic, unsaturated and heterocyclic aldehydes were selected to undergo the Hantzsch condensation in the presence of this heterogeneous

catalyst ($\text{HClO}_4\text{-SiO}_2$). The results of this study are summarized in (Table-1). It was indicated that both electron rich and electron deficient aldehydes as well as heterocyclic ones such as furfural, thiophene-2-carboxaldehyde, thiophene-3-carboxaldehyde and pyridine-3-carboxaldehyde worked well, mostly leading to high yields of products.

Table 1. $\text{HClO}_4\text{-SiO}_2$ Catalyzed Hantzsch condensation of polyhydroquinoline derivatives under solvent-free conditions

Entry	R	R ₁	R ₂	Time (min)	Product	Yield (%)	MP	MP (°C)
							(°C)	Reported
							Found	
1	C ₆ H ₅	CH ₃	OEt	8	4a	95	203-204	202-204 ²⁰
2	4-CH ₃ -C ₆ H ₄	CH ₃	OEt	12	4b	92	261-262	260-261 ²⁰
3	4-CH ₃ O-C ₆ H ₄	CH ₃	OEt	10	4c	96	256-257	257-259 ²⁰
4	4-Cl-C ₆ H ₄	CH ₃	OEt	10	4d	95	245-246	245-246 ¹⁶
5	4-NO ₂ -C ₆ H ₄	CH ₃	OEt	14	4e	90	243-244	242-244 ¹⁶
6	2,4-Cl ₂ -C ₆ H ₃	CH ₃	OEt	15	4f	92	242-243	241-243 ²⁰
7	2-Cl-C ₆ H ₄	CH ₃	OEt	13	4g	94	207-208	208-210 ¹⁶
8	3,4,5-(OCH ₃) ₃ -C ₆ H ₂	CH ₃	OEt	20	4h	89	199-200	198-199 ⁹
9	C ₆ H ₅ CH=CH	CH ₃	OEt	16	4i	90	204-205	204-206 ²⁰
10	2-NO ₂ -C ₆ H ₄	CH ₃	OEt	12	4j	89	206-207	206-208 ⁹
11	3-NO ₂ -C ₆ H ₄	CH ₃	OEt	14	4k	86	178-179	177-178 ⁹
12	4-F-C ₆ H ₄	CH ₃	OEt	10	4l	92	185-186	184-186 ²⁰
13	3,4, -(OCH ₃) ₂ -C ₆ H ₃	CH ₃	OEt	20	4m	95	198-199	-
14	4-N(CH ₃) ₂ -C ₆ H ₄	CH ₃	OEt	15	4n	90	262-263	263-264 ¹³
15	2- furyl	CH ₃	OEt	12	4o	92	247-248	246-248 ²⁰
16	2-thienyl	CH ₃	OEt	15	4p	96	239-240	238-240 ²⁰
17	3-thienyl	CH ₃	OEt	16	4q	91	246-247	248-250 ¹⁶
18	3-pyridyl	CH ₃	OEt	20	4r	94	66-67	66-67 ²⁰
19	4-OH-3-CH ₃ O-C ₆ H ₃	CH ₃	OEt	14	4s	89	211-212	210-212 ¹⁶
20	4-OH-C ₆ H ₄	CH ₃	OEt	18	4t	90	230-231	232-234 ²⁰
21	4-Br-C ₆ H ₄	CH ₃	OEt	16	4u	92	252-253	253-255 ²⁰
22	C ₂ H ₅	CH ₃	OEt	15	4v	83	145-146	145-146 ²⁰
23	n-C ₃ H ₇	CH ₃	OEt	13	4w	81	146-147	147-148 ²⁰
24	3,4,5-(OCH ₃) ₃ -C ₆ H ₂	CH ₃	OMe	20	4x	87	220-221	220-224 ⁹
25	4-N(CH ₃) ₂ -C ₆ H ₄	CH ₃	OMe	16	4y	85	257-258	258 ⁹

The structures of the products were determined from their spectroscopic (IR, ¹H NMR and MS) data.

However, aliphatic aldehydes afforded relevant lower yields (entry 22-23). All the products were identified by comparison of analytical data (IR, NMR and MS) with those reported of authentic samples.

Conclusions

In conclusion, we have developed a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation using a $\text{HClO}_4\text{-SiO}_2$ catalyst under solvent-free conditions. The mildness of the conversion, the experimental simplicity, the compatibility with various functional groups, the inexpensive reagents, the high yields and regioselectivity, the short reaction times and the easy workup procedure employed, makes this procedure very attractive to synthesize a variety of these derivatives.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded in KBr discs on a Bio-Rad win FT-IR spectrophotometer. $^1\text{H-NMR}$ spectra were recorded on a Varian Gemini 400 & 200 spectrometer. LCMS was recorded on a Agilent-1100 periods LC/ MSD (VL). Elemental analyses were performed on a Vario EL-III. TLC was carried out on GF₂₅₄ silica gel plates.

General experimental procedure. A mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and $\text{HClO}_4\text{-SiO}_2$ (50 mg) was heated at 90 °C with stirring for 8-20 min. and the solid product gradually formed. After completion of the reaction as indicated by TLC, the resulting solid product was treated with EtOAc followed by water and a brine solution and dried with anhydrous Na_2SO_4 . The solution was concentrated in vacuum to afford the crude product. The pure product was obtained by further recrystallization using absolute alcohol. The spectral and analytical data for selected compounds are presented below.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-fluorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate (4I). Yellow solid, mp 185-186 °C. IR (KBr): 3292, 2959, 1696, 1649, 1608, 1487, 1380, 1219, 1025, 764 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3): δ = 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.18 (t, J = 7.3 Hz, 3H, CH_3), 2.13-2.25 (m, 4H, 2 \times CH_2), 2.38 (s, 3H, CH_3), 4.05 (q, J = 7.33 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 5.8 (s, 1H, NH), 6.85-6.89 (m, 2H, ArH), 7.23-7.27 (m, 2H, ArH). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 14.1, 18.2, 26.4, 29.0, 32.1, 35.2, 50.1, 50.3, 59.0, 103.4, 110.0, 114.2, 114.3, 114.4, 129.0, 129.1, 144.1, 145.1, 149.4, 169.8, 194.2. LCMS: m/z = 356 (M-H)⁻. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_3\text{F}$: C, 70.58; H, 6.72; N, 3.92; F, 5.32. Found: C, 70.52; H, 6.79; N, 3.87; F, 5.28.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(3,4-dimethoxyphenyl)-5(6H)-oxoquinolin-3-carboxylate (4m). Yellow solid, mp 198-199 °C. IR (KBr): 3239, 2956, 1694, 1644, 1609, 1488, 1379, 1217, 1027, 753 cm^{-1} . ^1H NMR: (400 MHz, CDCl_3) δ = 0.95 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.21 (t, J = 7.3 Hz, 3H, CH_3), 2.19-2.35 (m, 4H, 2 \times CH_2), 2.38 (s, 3H, CH_3), 3.83 (s, 3H OCH_3), 3.81 (s, 3H OCH_3) 4.07 (q, J = 7.3 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 5.92 (s, 1H, NH), 6.70 (d, J = 8.30 Hz, 1H, ArH), 6.78 (dd, J = 8.30 and 1.96 Hz, 1H, ArH), 6.92 (d, J = 1.96 Hz, 1H, ArH). ^{13}C NMR (75 MHz, CDCl_3) δ 14.2, 18.2, 26.4, 29.1, 32.0, 35.0, 50.2, 50.5, 55.2, 55.3, 59.0, 103.8, 110.1, 111.4, 111.7, 119.2, 140.4, 144.5, 146.9, 147.9, 149.4, 166.9, 194.3. LCMS: m/z = 398 (M-H) $^-$. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_5$: C, 69.17; H, 7.26; N, 3.50; Found: C, 68.91, H, 7.30 N, 3.46.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxyphenyl)-5(6H)-oxoquinolin-3-carboxylate (4c). Yellow solid, mp 256-257 °C. IR (KBr): 3276, 2956, 1703, 1648, 1606, 1496, 1381, 1215, 1031, 765 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3), 2.01-2.10 (m, 4H, 2 \times CH_2), 2.30 (s, 3H, CH_3), 3.70 (s, 3H OCH_3), 4.00 (q, J = 7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.65 (d, J = 7.3 Hz, 2H, ArH), 7.10 (d, J = 7.3 Hz, 2H, ArH), 8.65 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1, 18.2, 26.4, 29.1, 32.1, 34.7, 50.2, 50.5, 54.8, 58.9, 103.2, 110.1, 113.0, 113.1, 128.2, 128.3, 139.8, 144.6, 149.1, 157.2, 166.9, 194.2. LCMS: m/z = 368 (M-H) $^-$. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_4$: C, 71.54; H, 7.31; N, 3.79; Found: C, 71.59; H, 7.35; N, 3.84.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-hydroxy-3-methoxyphenyl)-5(6H)-oxoquinolin-3-carboxylate (4s). Yellow solid, mp 211-212 °C. IR (KBr): 3388, 2953, 1700, 1643, 1589, 1482, 1385, 1218, 1029, 782 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 2.02-2.20 (m, 4H, 2 \times CH_2), 2.30 (s, 3H, CH_3), 3.80 (s, 3H OCH_3), 4.05 (q, J = 7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.60 (s, 2H, ArH), 6.82 (s, 1H, ArH), 7.69 (s, OH), 8.49 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.2, 18.2, 26.3, 29.2, 32.1, 35.0, 50.2, 55.4, 58.9, 104.0, 110.1, 112.0, 114.9, 119.3, 119.5, 139.0, 144.3, 144.5, 146.7, 149.2, 167.0, 194.3. LCMS: m/z = 384 (M-H) $^-$. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_5$: C, 68.57; H, 7.06; N, 3.64; Found: C, 68.52; H, 7.10; N, 3.60

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(2-chlorophenyl)-5(6H)-oxoquinolin-3-carboxylate (4g). Yellow solid, mp 207-208 °C. IR (KBr): 3063, 2956, 1721, 1640, 1611, 1467, 1384, 1227, 1021, 745 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.20 (t, J = 7.2 Hz, 3H, CH_3), 2.01-2.21 (m, 4H, 2 \times CH_2), 2.40 (s, 3H, CH_3), 4.05 (q, J = 7.2 Hz, 2H, CH_2), 4.60 (s, 1H, CH), 7.10-7.30 (m, 4H, ArH), 7.60 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.5, 29.1, 31.2, 32.3, 42.4, 46.8, 48.9, 50.5, 52.9, 55.1, 101.3, 109.2, 114.2, 125.9, 127.1, 128.7, 131.1, 132.3, 141.0, 167.5, 195.7. LCMS: m/z = 372 (M-H) $^-$. $\text{C}_{21}\text{H}_{24}\text{NO}_3\text{Cl}$: Anal. Calcd for C, 67.56; H, 6.43; N, 3.75; Cl, 9.38; Found: C, 67.52; H, 6.48; N, 3.72; Cl, 9.42

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